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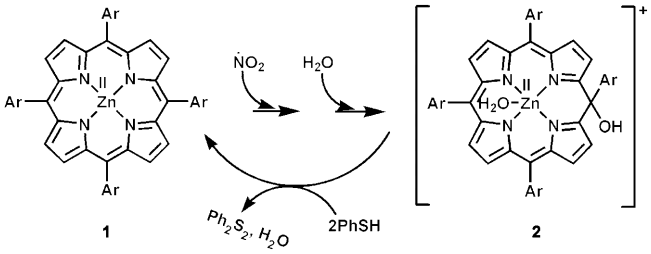
Oxidative Degradation of Zinc Porphyrin in Comparison with Its Iron Analogue

Jagannath Bhuyan and Sabyasachi Sarkar*[a]

Isoporphyrins, derivatives of porphyrins possessing a saturated *meso*-carbon, are known to be reactive intermediates in the biosynthesis of chlorophyll and byproducts of heme oxidation.[1] They are unique because of their distinctive near-IR electronic absorption with interesting redox behavior.[2] Based on the proposal of isoporphyrin as a tautomer of porphyrin by Woodward,[3] Dolphin and co-workers reported the formation of metalloisoporphyrin by electrochemical oxidation of zinc *meso*-tetraphenylporphyrin (**1**).[4] These tetraaryl metalloisoporphyrins were never isolated in the pure state, although they have been known to exist in solution for the last four decades.[5] Therefore, structural features of such macromolecules remained unexplored. While investigating the joint role of biorelevant molecules like O_2 and NO in creating oxidative stress we found *meso*-hydroxylation of an iron porphyrin that follows degradation similar to that of heme proteins.[6] Heme oxygenase catalyzes the degradation of heme to biliverdin by *meso*-hydroxylation as the first step using oxygen along with nicotinamide adenine dinucleotide phosphate (NADPH) and cytochrome P450 reductase.[7] In such a degradation reaction, the redox role of iron ion has not been properly stressed. For chlorophyll, the degradation may be photooxidative or enzymatic as known along with different environmental stress-related degradation.[8] As most of the isoporphyrin chemistry in solution is studied by non-redox zinc systems, we now investigate zinc porphyrin chemistry similar to those studies conducted with iron systems.[6] Based on this, herein we report the first structural characterization of an air-stable tetraarylzinciso-porphyrin. Interestingly, it does not decompose to a biliverdin-type complex like its iron analogue, which stresses the very distinctive role of a specific metal in metallo-macromolecules in their degradation processes.

Compound **1** in CH_2Cl_2 reacts with nitrogen dioxide (NO and O_2) to yield the zinc hydroxyisoporphyrin (**2**; Scheme 1), which was isolated like its iron analogue.[6] The molecular structure[9] of **2** is shown in Figure 1. The presence of the counteranion nitrate and the tetrahedral *meso*-carbon (C5) confirms the cationic nature of **2**. One oxygen atom of counteranion nitrate is hydrogen bonded with the oxygen



Scheme 1. Synthesis of hydroxy isoporphyrin (**2**) from **1** and the regeneration of **1** using thiol. The counteranion NO_3^- in **2** is not shown.

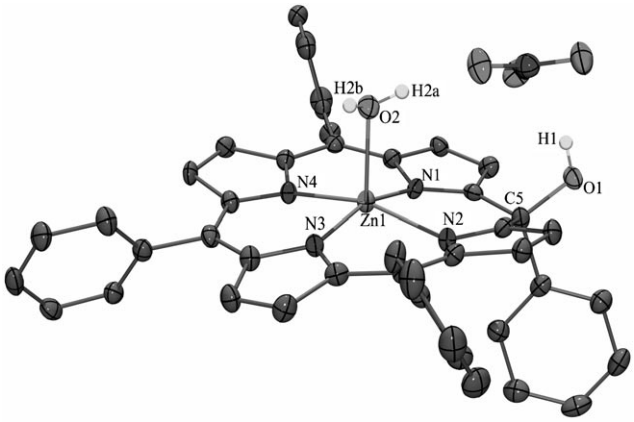


Figure 1. ORTEP view of **2** showing 50% probability thermal ellipsoids. Hydrogen atoms except those at O1 and O2 are omitted for clarity. Selected bond lengths and angles: C5–O1 = 1.430(4) Å, Zn–O2 = 2.064(3) Å; C5-O1-H1 = 109.4(3)°.

[a] J. Bhuyan, Prof. S. Sarkar
Department of Chemistry, Indian Institute of Technology Kanpur
Kanpur-208016, U.P. (India)
Fax: (+91) 512-259-7265
E-mail: abya@iitk.ac.in

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atom of *meso*-hydroxyl group of the isoporphyrin and another oxygen atom of the nitrate is hydrogen bonded with the oxygen atom of the water molecule coordinated to the zinc atom. (Figure S7 in the Supporting Information).

In **2** all of the carbon atoms attached to C5 show bond-length elongation (Figure S8 in the Supporting Information).[9] The C4−C5 and C5−C6 bond lengths are around 1.505 Å, equivalent to a single bond, showing the point of disruption of aromaticity in **2**. There is also an increase in the C5−C21 bond length. The C4-C5-C6 angle decreases to 117° compared with the other three *meso*-carbon angles (125°). Interestingly, upon hydroxylation the macrocyclic structure became significantly ruffled with the *meso*-carbon atoms moving above and below by 0.42, −0.22, 0.169, and −0.20 Å at C5, C10, C15, and C20, respectively, but such ruffling was not observed in the iron isoporphyrin.[6] The loss of its aromaticity is also corroborated by a distinctive NMR spectrum, in which the β-H peaks of pyrrole are observed in the region $\delta = 6$–7 ppm (Figure S4 in the Supporting Information).

The electrochemistry of **2** differs much from the starting complex **1**. Its first reduction potential (irreversible) appears at a very low potential, E_{pc} (−115 mV vs. Ag/AgCl) (Figure S6 in the Supporting Information) to suggest its ease for reduction under mild conditions. Thus, compound **2** can be reduced to the starting complex **1** with ease even using thiophenol (Figure 2, Scheme 1). However, upon addition of pyridine the first irreversible reduction was now shifted to a reversible reduction at −40 mV (vs. Ag/AgCl). Such dramatic effect of pyridine to facilitate reduction may be due to its coordination to zinc, but its exact role to bring such changes is yet to be ascertained. Interestingly, the formation of a stable iron β-pyridiniumtetraphenylporphyrin, a very unstable iron isoporphyrin and an iron porphodimethene as the reaction products of iron porphyrin cation radical with pyridine is reported.[10] Being iron complexes, these are prone to have metal- and ligand-centered redox reactions. Recently, the electrochemistry of some iron phorphodimethene complexes showed that the ligand-based redox reaction requires high potential.[11] In the present case such reversible reduction under the influence of pyridine may be related to its coordination to zinc, presumably replacing the coordinated water in **2**.

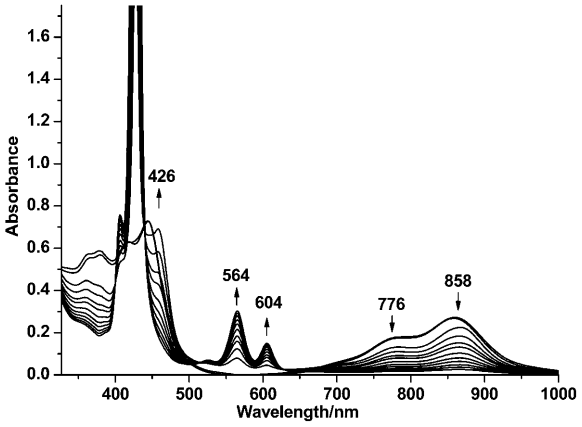

Figure 2. Reduction of **2** to **1** in dichloromethane by thiophenol (trace pyridine; time interval of each scan, 2 min).

DFT calculations[12–13] of **2** (Figure 3) clearly show the disruption of delocalization around the C5 atom in the HOMO. The narrow HOMO–LUMO gap corroborates the appearance of a low-energy electronic transition in the near infrared region (Figure 2).

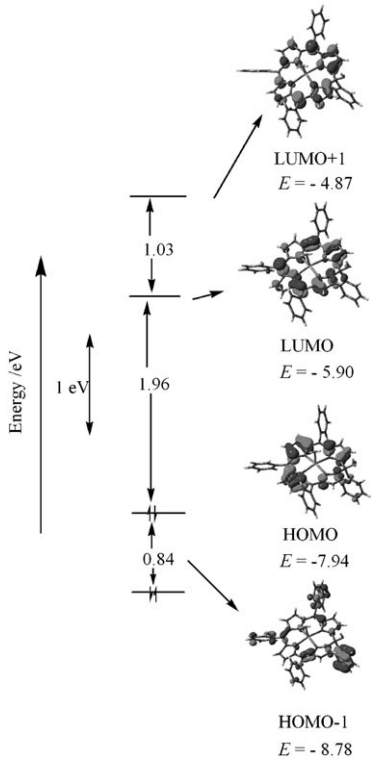

Figure 3. Relative energy-level diagram for the selected molecular orbitals of **2**. Isosurface cutoff value = 0.04.

Nitrogen dioxide may form by the reaction of free O_2 and NO during malfunction of oxygenation and NO synthase reactions.[14] This is also a product of the spontaneous decay of peroxynitrite, which is the most damaging reactive species produced by the reaction between superoxide ion and nitric oxide.[15] Most metallated macromolecules present in the natural systems function as antioxidants to smother the onslaught of reactive oxygen and nitrogen species. It is now known that metalloporphyrin and metallocorrole complexes have high utility to catalyze the decomposition of these reactive oxygen and nitrogen species.[16]

The degradation of closed-shell metalloporphyrin by non-biological oxidizing agents, such as cerium(IV) or thallium(III) salts, led to the formation of several products.[17] Under such drastic oxidizing conditions, less amount of biorelevant degraded product was obtained. Further, there are reports that magnesium porphyrins are photochemically oxidized to produce the corresponding ring-opening compound that

mimics the major biochemical process of chlorophyll degradation.[18] Therefore, there is distinctively different chemistry associated with iron-based heme degradation and magnesium-based chlorophyll degradation. The formation of a stable octaethyloxophlorin radical from the oxidation of zinc octaethyloxophlorin dianion has been reported.[19] Surprisingly, unlike the corresponding iron isoporphyrin, compound **2** remained stable in CH_2Cl_2 or toluene under the exposure of laboratory light even in the presence of O_2. This clearly shows the redox role of iron in degrading the heme to verdoheme.[6] Such a difference in chemistry stresses the obligate redox role of iron in the event of malfunctioning of heme oxygenase and nitric oxide synthase, resulting heme degradation process. Interestingly, compound **2** is quantitatively photoreduced by direct sunlight to **1** under an argon atmosphere without any photodegradation (Figure S2 in the Supporting Information). However, in air it does degrade under bright sunlight exposure.[20] The present study shows that in the absence of either oxygen or light, a highly oxidized porphyrin ring, such as that present in **2** does not undergo porphyrin degradation when coordinated to a non-redox metal like zinc. Thus, compound **2** is relatively stable and unlike its iron analogue[6] it does not undergo degradation in aerobic conditions. It readily responds to chemical or photoreduction to revert back to the starting complex **1**. This work relates that in the catabolism of heme proteins, the reactions must involve complimentary changes in the redox states of the coordinated iron concomitant with the changes in macromolecules. However, the reaction of **1** under oxidative stress may lead to the formation of oxidized **2**, but to induce chlorophyll-like degradation the presence of strong light, such as sunlight is essential.[18,20]

In summary, zinc hydroxyisoporphyrin (**2**) has been structurally characterized as the oxidative product of zinc *meso*-tetraphenylporphyrin (**1**) after exposure to NO_2 (NO and O_2). Compound **2** does not respond to degradation reactions in the same way as its iron analogue and requires strong light exposure under oxygen to degrade.

Experimental Section

The synthetic details, characterization (UV/Vis, NMR spectra, cyclic voltammetry, X-ray structural data), and DFT details of **2** are provided in the Supporting Information. CCDC-772725 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] See the Supporting Information for synthetic details. Crystallographic data for **2**: $C_{44}H_{31}N_5O_5Zn$, $M_r=775.09$, $0.20\times0.10\times0.08$ mm^3, monoclinic, $a=12.910(5)$ Å, $b=11.244(5)$ Å, $c=24.241(5)$ Å, $\alpha=90.005(5)°$, $\beta=92.287(5)°$, $\gamma=90.005(5)°$, $V=3516.0(2)$ Å^3, space group $P21/c$, $Z=4$ $R_1=0.0603$ $\lambda(Mo_{K\alpha})=0.71073$ Å, $T=100(2)$ K, 22805 reflections, 8660 unique, $R_{int}=0.0838$, $R_1=0.060$, $wR_2=0.137$.

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[12] DFT calculations have been carried out by employing a B3LYP hybrid functional using the Gaussian 03 program. Molecular orbitals were visualized by using GView. The 6-31G*+ basis set was used for C, N, O, and H atoms, and the effective core potential basis set LanL2DZ was used for the Zn atom. The geometry of **2** was taken from the crystal structure.

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[20] Under prolonged direct exposure of sunlight in the presence of air **2** degrades in toluene to a zinc biliverdin type complex along with several other unidentified products.

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